5. The oxygen chamber is a very effectual way of giving oxygen, especially in chronic cases, but it involves much expense and care.

6. An extremely useful and effectual appliance for the administration of oxygen is Meltzer's apparatus for oral insufflation.

NOTE.—In the *British Medical Journal* March 6, 1920, Dr. J. C. Meakins shows that the arterial blood of the normal individual is nearly 5 per cent. "undersaturated" with oxygen, while in pneumonia the "undersaturation" may amount to nearly 18 per cent. By giving oxygen with the Haldane apparatus he was able to reduce the degree of undersaturation in the normal by one-half and in the pneumonic individual to just over 3 per cent. In other words, by the use of the method he increased the oxygen content of the blood of the cyanosed pneumonic person to above that of the normal individual. No better evidence than this could be needed of the value of oxygen inhalation in anoxemia.

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# A CASE OF SPLENOMEGALY WITH POLYMORPHONUCLEAR NEUTROPHIL HYPERLEUKOCYTOSIS.

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IN the November number, 1919, of this JOURNAL, p. 618, Dr. H. Z. Giffin, of the Mayo Clinic, presented a case of "Persistent Eosinophilia with Hyperleukocytosis and Splenomegaly." As soon as this article appeared I immediately recalled a patient we had treated with curiously corresponding findings: a very large spleen; a very high leukocyte count markedly increasing after splenectomy; a gradual decrease in number thereafter, with marked constitutional improvement. Comparing the two cases the most striking difference appeared in the type of the leukocytes: Giffen's case presented marked and persistent eosinophilia; in our case there was an overwhelming preponderance of mature polymorphonuclear neutrophils. It is suggested to the reader that Giffin's article be reviewed in order to compare the two reports. His thorough search of the literature dealt largely with eosinophil leukocyte increase. It is notable, however, that he found in a thorough search of the literature little at all comparable with his case. I wish to present the following data, acknowledging that I have not consulted the Surgeon-General's Library nor made a thorough review of the literature; but that portion immediately available has shown nothing corresponding whatever except Giffin's report.

CASE HISTORY.—C. D., aged fifty-eight years; female; married; two daughters living and well. She was first seen November 21, 1917.

*Family History.* Negative.

*Past History.* Stated that she had acute arthritis at sixteen, but nothing eventful thereafter until signs of the menopause developed at forty, when she discovered she had uterine prolapse.

*Present Complaint.* On May 3, 1917, she developed severe pain in the left side. The physician who was called stated he found a large spleen. She was in bed four days and thought she had fever. The pain recurred at intervals, and each time she thought fever recurred. Four days before coming to the office she found difficulty in lying down or stooping or making any considerable movement of the body; cough or deep breathing gave much distress. She had lost twenty pounds in weight since the onset of this complaint, but had been up and around doing her work much of the time.

*Physical Findings.* Patient looks thin, tired and in evident distress. A very large tumor was found in the upper left quadrant, extending diagonally downward and toward the right, three inches beyond the navel and having the general characteristics of an enlarged spleen. It was very tender to pressure and the pain increased on movement. No spleen notch could be identified. General examination of the chest was negative. The fluoroscope showed some fixation of the left side of the diaphragm. It also showed the stomach crowded over to the right; the colon was not studied. Pelvic examination uncovered a pessary which she had worn for fourteen years. When this was removed the cervical area looked very angry, and it left some bleeding. Retroperitoneal septic accumulation was thought of, but the temperature was normal and nothing else corroborated such a hypothesis. Furthermore, after three days in the hospital, with vaginal douches, the local condition entirely cleared up. The blood showed a picture strikingly different than might have been expected from a splenomyelogenous leukemia. The first leukocyte count showed 65,000. The blood smears showed an overwhelming predominance of well-formed adult type polymorphonuclear neutrophil cells. After three days' rest in bed and symptomatic treatment the second leukocyte count showed 45,000.

Photomicrographs (Figs. 1 to 3), with lower, medium and higher magnification, show strikingly well the form of the leukocytes. The neutrophil granules took on the customary stain with Wright's stain, but the eosinophils were difficult to find, as were also the small lymphocytes. An average differential count showed: Polymorphonuclears, 99 per cent.; large lymphocytes, 0.5 per cent.; eosinophils, 0.5 per cent.; an occasional normoblast; 200 cells were counted. This relationship continued in all the differential counts made. Red-blood count showed 4,200,000 and hemoglobin 80 per cent. when the patient was first seen.

After continuing, with much discomfort and abdominal distress, operation was advised and carried out by Dr. W. A. Coventry, of this clinic, on December 3, 1917:

"A large spleen was found, strongly adherent to the diaphragm above and separated from the stomach wall with great diffi-

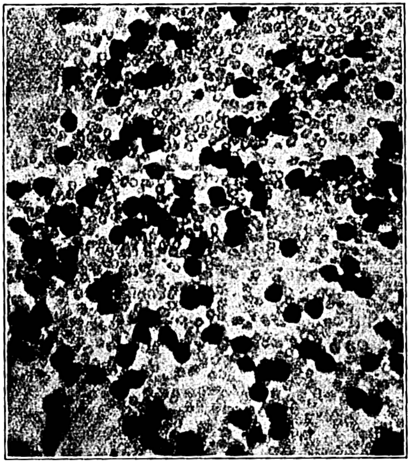

FIG. 1.—Photomicrograph of blood smear, showing the very large number of leukocytes in proportion to the red blood cells.

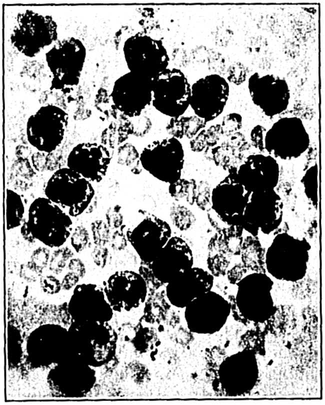

FIG. 2.—Photomicrograph with higher magnification, showing very well the nuclear structure and giving a suggestive outline of the granules.

culty. Sutures had to be placed in the outer wall of the stomach to close a possible defect. A decided perisplenitis accounted for these adhesions, particularly above and behind. The operation resulted in considerable shock so intravenous saline and other methods of stimulation were resorted to. After the second day recovery was uneventful except for some slight wound drainage, beginning after the sixth day and lasting for a week."

A decided increase in the leukocytes followed almost immediately after the operation. On December 6, 1917, the count was 240,000; on December 8 it was 175,000. This increase of about sixfold, while large, is not so greatly out of proportion as might appear, since splenectomy or even hysterectomy has been known to transiently increase a low count to a similar degree. The count on December 12 was 50,000; at the time of leaving the hospital, December 29, the count was 45,000. She was able to walk around easily, had lost much of her nervousness and was eating well.

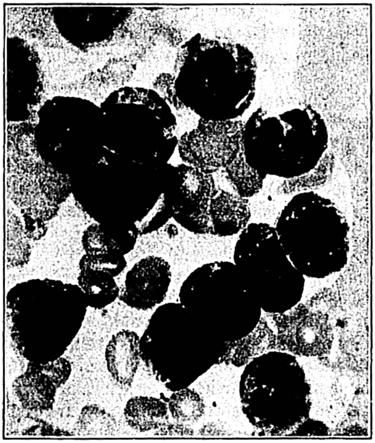

FIG. 3.—Photomicrograph with still higher magnifications and beautifully showing the adult type of well-formed nuclei and also showing granules.

She went away some distance to her home. We had no opportunity for further blood counts, but her daughter reported, from time to time, a rapid improvement in her health, increase in strength, and that she had again assumed her usual household duties.

When she was again seen it was by one of my associates, and at a time when we were having the epidemic of streptococcus lung infection that occurred in the spring of 1918. She entered the hospital on April 27, 1918, in a comatose condition. She had then been sick about one week. Massive dulness was reported over the bases of both lungs, more on the left than on the right. She was raising bloody, frothy material and died within two hours. An autopsy was not permitted and her sudden death made procrastination in getting blood smears particularly unfortunate.

**Discussion.** The data in this case are lacking in many points of interest. The persistent increase, however, in adult polymorphonuclear leukocytes, associated with splenomegaly was so definite as to merit an analysis of the factors concerned. It requires courage to plunge into any discussion involving the spleen; in so doing we are easily led into a consideration of controversial matter. However, certain light seems to be thrown on the spleen function in the presence of hyperactivity in the bone-marrow yielding an excessive number of leukocytes (even though of normal forms) in the circulating blood.

In the embryo, up to the fourth month of fetal life, both the spleen and bone-marrow form red blood cells; both, together with certain lymph gland and lymph-adenoid tissue, possibly also the liver, form myeloblasts. After the fourth month of fetal life both erythroblasts and myeloblasts are formed almost entirely in the bone-marrow. Thereafter, physiologically and pathologically, we may state that the bone-marrow and the spleen, *in the process of blood regeneration and destruction, work coördinately.*

The normal disposition of incapacitated red blood cells seems to be accomplished largely through the filtration or sieve-like action of the spleen pulp, the discarded material being carted to the liver and becoming the ultimate source of pigment in the bile. Obsolete polymorphonuclear leukocytes seem to meet a similar fate, although probably a large number, particularly when called forth by localized inflammation or other chemotactic influences, are cast off from the body in the form of discharges, such as is seen in purulent sputum, discharging abscess or in pyelocystitis producing pyuria. But when we know that the bone-marrow is hyperfunctioning for considerable periods of time without known avenues of escape for either the excess of red or white cells it seems logical to assume there will be an overfunction of the spleen, with enlargement. Incidentally, we may remark that much more is known concerning the general method of erythrocyte destruction and replacement than of the similar process obtaining for leukocytes.

A consideration of certain well-known pathological entities illustrates well the position taken by the spleen and further demonstrates its response to varying degrees of activity in the bone-marrow. This must be considered for the time being totally regardless of the ultimate etiological factors controlling hematopoietic function:

1. We do not find spleen enlargement in the presence of a severe secondary anemia, for example, that caused by carcinoma of the stomach, with gradual enteric bleeding.

2. In the severest types of fulminating pernicious anemia (aplastic), with fatigued, overtaxed and hypoplastic bone-marrow, we have no spleen or liver enlargement.

3. It is difficult with our present knowledge to speak dogmatically concerning the constancy of spleen hyperfunction in so-called idiopathic pernicious anemia. However, with the H-H index,[1] over one and higher, as elicited by a determination of pigment values in the duodenal contents, and with a patient showing an icteric tendency, spleen enlargement is usually demonstrable.

4. In Vaquez's disease splenomegaly is one of the triad of symptoms upon which the diagnosis is made; the liver is choked with blood-derived pigment.

5. In the anemia of hemolytic icterus, whether familial or acquired, the results of hyperactivity in the bone-marrow are lost through the hyperfunctioning of the enlarged spleen; dramatically enough the disease is cured by splenectomy. This is true whether the inherent stimulus to overdestruction resides in the spleen itself or whether that organ is the unwitting agent of some extraneous factor.

6. The same principle holds with that group of anemias loosely classified as "splenic anemia." When localized spleen disease, notably syphilis or tuberculosis, has been proved, persistent and extreme secondary anemias have been promptly ameliorated by splenectomy.

The inference is left by W. J. Mayo, in an excellent article developing the surgical indications for splenectomy,[2] that the remaining anemias in this group, however named, represent similar splenic processes as yet unknown and unidentified. The abdominal conditions associated with cirrhosis of the liver are similarly given plausible consideration and the splenic factor in visceral circulation analyzed.

7. There is a conversational opinion expressed occasionally by men of experience that myeloid leukemia or myelocythemia represents a malignant overproduction of the bone-marrow, resulting in primitive cell forms, sarcomatous in nature, flooding the circulation. It is true that when this disease is well developed the whole hematopoietic system is involved. Then it is that leukemic tumors may be found in almost any tissue, definitely metastasizing. The much enlarged spleen led to the earlier conclusion that these metastatic agglomerations therein became the source of many of the forms in the blood. The early course of the disease, nevertheless, points strikingly to the attempt on the part of the spleen to exercise the basic function of the pulp spaces to keep these abnormal elements out of the blood, for the same reason as they engulf the broken-down and damaged erythrocytes in malaria. Hence it is that the Mal-

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[1] Schneider, J. P.: Further Quantitative Study of Duodenal Blood-derived Pigments, Arch. Int. Med., 1917.

[2] Mayo, W. J.: Ann. Surg., July, 1919.

pighian corpuscles are pushed aside and the pulp spaces become clogged with masses of myeloblastic elements. As further supporting this screen function of the spleen we have:

(*a*) In the few cases of myeloid leukemia in which splenectomy has been performed the accessory spleens and lymph gland tissues have undergone hyperplasia.

(*b*) In following the direct vascular connection beween the spleen pulp and the liver (well illustrated by pigment deposition in the liver in active pernicious anemia) we see the reason for the earliest, exquisite evidence of invasion of the general tissues in myeloid leukemia (just as in lymph-gland enlargement in the drainage area of the breast in carcinoma the glands withstand the brunt of the invasion, until they are overwhelmed).

There is, therefore, striking argument in support of the general assumption that the spleen exercises physically and pathologically a filtering or screen capacity. At operation in this case there was no indication of liver involvement or glandular enlargement; in other words, nothing to indicate that the spleen was overrun or overpowered. This case, even more than Giffin's, would seem to indicate that under certain conditions there can be a calling forth of particular types of leukocytes, normal in form and structure, without any apparent tendency to ultimate failure on the part of the bone-marrow (as shown by a mobilization of embryonal or immature forms), seeming to exemplify the ability of the bone-marrow to hyperfunction in a benign way. What the chemotactic irritant was in this case must remain unsolved. Splenomegaly, as might be expected, took place to a marked degree. It appears more likely that the massive adhesions about the spleen were the result of hyperactivity and congestion in that organ, with overgrowth of connective tissue rather than the inherent cause of the leukocytosis itself. The long-continued irritation due to the wearing of the pessary is only one possibility and the usual possibilities of focal infection come to mind. Indeed, the ultimate mechanism or device which stimulates or restrains the bone-marrow in its degrees of activity, depending on bodily needs, is poorly understood. It is known that different types of leukocytes appear in the blood under the influence of varying irritants or infections, such as eosinophilia in trichinosis and an increase in large lymphocytes in malaria or pertussis. But wherever this control may be found, ultimately to lie it probably follows the rule of other physiological processes: a definite sequence of events transpiring whenever certain elemental stimuli are given recognition. This makes it possible for the ensuing circle of events to be broken in any portion of the chain and the disease picture that results must vary greatly, depending on the position and type of the break. The disturbance of one segment of the hematopoietic system yields lymphatic leukemia or Hodgkin's; overstimulation of the bone-marrow from as yet unknown sources produces another picture. But whether the end-products of this hyperfunction, circulating in the blood produce the picture of hyperleukocytosis or a leukemia must depend on whether the myeloblastic production is lawful and benign, or Bolshevistic and malignant. In either case splenomegaly can be expected. *The spleen and bone-marrow hyperfunction coördinately.*

For H. Z. Giffin's kindly interest in this case and his opinion and studies of the blood slides as well as the making of the photomicrographs, I wish to acknowledge my deep indebtedness.

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# A COMPARATIVE STUDY OF THE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.

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AND
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As the result of comparative therapeutic tests conducted by Hata[1] in hen spirillosis and with mice infected with S. obermayeri, Ehrlich announced that 0.9 gram neosalvarsan possesses the curative value of 0.6 gram salvarsan; from the practical standpoint of treatment in syphilis this subject is of great importance, and particularly so by reason of the opinions held by several syphilographers of experience that neoarsphenamine in the amounts commonly administered (0.6 to 0.9 gram) does not appear to possess the same therapeutic activity as arsphenamine (0.4 to 0.6 gram).

**Purpose of Investigation.** In our experiments conducted for the purpose of ascertaining the comparative therapeutic activity of arsphenamine and neoarsphenamine, we utilized rats infected with a virulent strain of T. equiperdum, to ascertain the smallest amounts of arsphenamine and neoarsphenamine, produced by other laboratories and by ourselves, that would sterilize animals infected twenty-four hours before with intraperitoneal injections of approximately known numbers of trypanosomes. Inasmuch as the trypanosomes in the control animals appeared in the peripheral blood within forty-eight hours and caused death in from the fifth to seventh day, these experiments yielded quite sharp and definite results, although constituting a severe test of the therapeutic activity of the compounds.

A second purpose of these studies was to determine whether differ-

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[1] The Experimental Chemotherapy of Spirilloses, Rebman, London, 1911.